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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,509	06/25/2001	Fritz Grunert	24741-1523	9439

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,509	GRUNERT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-12 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-12, and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 10/20/03 has been entered. Claims 7, 13, and 14 have been canceled. Claims 1-6, 8-12, and 15-17 are currently pending in the instant application. An action on the merits follows.

The text of those sections of Title 35, US code, not included in this office action can be found in previous actions.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1-6, 8-12, and 15-17 under 35 U.S.C. 112, second paragraph, for the omission of essential steps is withdrawn in view of applicant's amendments to the claims.

The rejection of pending claims 1-6, 8-12, and 15-17 under 35 U.S.C. 112, second paragraph, for indefiniteness is maintained in part. The previous office action stated that the phrase "wherein the expression vector employed for the genetic immunization in step (b), .." in claim 1 lacked antecedent basis for "the expression vector". While applicant has amended claim 1 to indicate that the DNA encoding the polypeptide is cloned into an expression vector, the applicant has also amended the phrase quoted above to recite, " the expression vector employed for genetic immunization in step (**c**) ". Since the genetic immunization step is step (b), not step

(c), the claim as amended is confusing . The applicant can overcome this rejection by amending line 12 of claim 1 to recite "... immunization in step (**b**).....".

Claim Rejections - 35 USC § 103

The rejection of pending claims 1-6, 8-12, and 15-17 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,773,293 (6/30/98), hereafter referred to as Kilgannon et al., in view of U.S. Patent No. 5,736,524 (4/7/98), hereafter referred to as Content et al., and further in view of Letesson et al. (1997) Clin. Diag. Lab. Immunol., Vol. 4, 556-564 and Whitehorn et al. (1995) Bio/Technology, Vol. 13, 1215-1219, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that a novel feature of their invention is the use of transiently transfected cells which express a polypeptide linked to a GPI anchor as a "solid support" for antibody binding and detection, rather than the use of isolated polypeptides. In response, please note that the claims as amended are not limited to use of the transiently transfected cells as a support for the polypeptide in the binding assay. Step (c) of claim 1, recites that the antibodies formed in step (b) are removed from the animal and reacted with the polypeptide formed in step (a). Step (a) reads broadly on the transient expression of a polypeptide that can be present transiently at the cell surface via a GPI anchor. Thus, step (a) as written reads on expressed polypeptide which may or may not be associated with the cell, as the presence of the polypeptide

at the cell surface is only transient. Since step (c) refers to the polypeptide, and not a cell expressing the polypeptide, it is clear that the claims read on both alternatives.

In regards to the cited prior art, the applicant has presented arguments against each reference individually. In response, please note that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Further, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Also, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. In the instant case, the rejection of record is based on the combined teachings of Kilgannon et al. Letesson et al., Whitehorn et al., and Content et al.

The primary reference cited in this rejection is Kilgannon et al. The applicant argues, " now that claim 1(a) has been excluded, the Kilgannon patent has no more relevance to the new claim 1 (a)" (Applicant's response, page 7). It is unclear what the applicant means by stating that claim 1 (a) has been "excluded". If the applicant means that step (a) in claim 1 has been amended to recite a specific GPI anchor not taught by Kilgannon, then the office responds that Kilgannon was cited for teaching ICAM-4/GST fusion proteins wherein the GST can be used as a detection signal for detecting the ICAM-4 fusion protein, and the use of those fusion proteins

to generate antibodies *in vivo* and to detect anti-ICAM antibodies *in vitro* (Kilgannon et al., columns 7-16). The previous office action clearly stated that while Kilgannon et al. teaches that the detection signal in the fusion protein is GST, the use of epitope tags such as hexa-histidine or **GPI residues** was well known at the time of filing as evidenced by the teachings of Letesson et al. and Whitehorn et al. In particular, Whitehorn et al. was cited for teaching recombinant fusion protein containing a GPI anchor at the C-terminus useful for detecting/purifying the fusion protein following cleavage of the GPI anchor (Whitehorn, page 1215). Whitehorn et al. also provides motivation for using the GPI residue tag sequence to bind the polypeptide to a solid surface using antibodies which recognize the tag sequence, and for using the GPI polypeptide to detect antibody binding to the polypeptide of interest. Thus, the teachings of Whitehorn supplement the teachings of Kilgannon et al. and provide motivation for substituting a GPI anchor for GST. Applicant's argument that Whitehorn isolates the polypeptide using phospholipase C cleavage and that the instant method do not require polypeptide isolation is not compelling since the claims as written do not exclude the use of isolated or cleaved polypeptide to bind to the antibody in step (c).

Applicant's comment that Letesson et al. has no relevance to new claim 1(a) is also confusing since Letesson et al. was cited to supplement Kilgannon et al. by teaching the use of hexa-histidine peptides as detection tags in recombinant fusion proteins and use of the tagged fusion proteins in antibody binding assays (Letesson et al., pages 557-558). Claim 3 continues to recite that the detection tag is a hexa-histidine tag.

Regarding the teachings of Content et al., the applicant argues that the test system taught by Content et al. requires the binding of expressed polypeptide to a solid support and that the

instant methods use transiently transfected cells as a solid support system. However, as noted above, the instant claims as written are not so limited, and continue to read on the use of polypeptide which is not present at the cell surface of the transiently transfected cell. Content et al. was cited in the previous office action to supplement Kilgannon et al., Letesson et al., and Whitehorn et al., by teaching the generation of antibodies *in vivo* in mice by direct administration of a DNA plasmid vector encoding a polypeptide of interest (Content et al., columns 10-13 and 17). Content et al. was further cited for teaching that vectors encoding a polypeptide operatively linked to the CMV promoter and BGH transcriptional termination sequence (polyA sequence) can be used not only to express the polypeptide *in vivo*, but also to produce the protein in cells *in vitro* (Content et al., columns 10-14). In particular, Content et al. teaches that polypeptide produced by transfecting mammalian cells *in vitro* can be bound to a solid support and used in immunoassays to bind antibody specific for the polypeptide (Content et al., columns 14 and 16-17).

Content et al. was further cited for providing motivation to use eukaryotic vectors instead of protein to generate antigen specific antibodies *in vivo.* Content teaches that its better to immunize with a gene rather than a gene product for the following reasons: 1) the simplicity with which native or nearly native antigen can be presented to the immune system using genetic immunization, and 2) the fact that mammalian proteins expressed recombinantly in bacteria for use as antigens in mammals often require extensive treatment to insure appropriate antigenicity (column 9, lines 60-66). In view of the motivation provided by Content et al. to use a gene rather than a gene product to produce antibodies *in vivo*, it would have been *prima facie* obvious to use a DNA encoding a polypeptide linked to a detection tag such as GPI or hexa-histidine in the

methods of immunizing taught by Kilgannon et al. as supplemented by Letesson et al. and Whitehorn et al. rather than a polypeptide made in bacteria. Further, in view of the motivation provided by Content et al. to use polypeptide produced from mammalian cells instead of bacterial cells, it would have been *prima facie* obvious to the skilled artisan to substitute eukaryotic vectors and cells for the bacterial vectors and cells used in Kilgannon et al. to produce the polypeptide *in vitro*. In addition, based on the high level of skill in the art of molecular biology and the specific teachings in Content as to mammalian expression vectors useful for both producing antibodies *in vivo* and producing protein in mammalian cells *in vitro*, the skilled artisan would have had a reasonable expectation of success in modifying the expression vectors taught by Content et al. to include the polypeptide fusion proteins taught by Kilgannon et al., Letesson et al., and Whitehorn et al., and in using the modified vector to generate antibodies *in vivo* and in producing protein in mammalian cells *in vitro* useful for detecting the antibody by immunoassay.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Please note that the United States Patent and Trademark Office will begin to move to the new campus in Alexandria, Virginia, in December 2003. The examiners of Art Unit 1632 will be moving in January 2004. As of January 13, 2004, this examiner's phone number will be (571) 272-0737, and that of the examiner's supervisor will be (571) 272-0734.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER